



Voltage-gated calcium channels: Determinants of channel function and modulation by inorganic cations



Felix Neumaier^{a,*}, Maxine Dibué-Adjei^{a,b,c}, Jürgen Hescheler^a, Toni Schneider^{a,*}

^a Institute for Neurophysiology, University of Cologne, Robert-Koch-Str. 39, 50931 Cologne, Germany

^b Department for Neurosurgery, Medical Faculty, Heinrich Heine University, Moorenstraße 5, 40225 Düsseldorf, Germany

^c Center of Molecular Medicine, Cologne, Germany

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ABSTRACT

Voltage-gated calcium channels (VGCCs) represent a key link between electrical signals and non-electrical processes, such as contraction, secretion and transcription. Evolved to achieve high rates of Ca²⁺-selective flux, they possess an elaborate mechanism for selection of Ca²⁺ over foreign ions. It has been convincingly linked to competitive binding in the pore, but the fundamental question of how this is reconcilable with high rates of Ca²⁺ transfer remains unanswered. By virtue of their similarity to Ca²⁺, polyvalent cations can interfere with the function of VGCCs and have proven instrumental in probing the mechanisms underlying selective permeation. Recent emergence of crystallographic data on a set of Ca²⁺-selective model channels provides a structural framework for permeation in VGCCs, and warrants a reconsideration of their diverse modulation by polyvalent cations, which can be roughly separated into three general mechanisms: (I) long-range interactions with charged regions on the surface, affecting the local potential sensed by the channel or influencing voltage-sensor movement by repulsive forces (electrostatic effects), (II) short-range interactions with sites in the ion-conducting pathway, leading to physical obstruction of the channel (pore block), and in some cases (III) short-range interactions with extracellular binding sites, leading to non-electrostatic modifications of channel gating (allosteric effects). These effects, together with the underlying molecular modifications, provide valuable insights into the function of VGCCs, and have important physiological and pathophysiological implications. Allosteric suppression of some of the pore-forming Ca_vα₁-subunits (Ca_v2.3, Ca_v3.2) by Zn²⁺ and Cu²⁺ may play a major role for the regulation of excitability by endogenous transition metal ions. The fact that these ions can often traverse VGCCs can contribute to the detrimental intracellular accumulation of metal ions following excessive release of endogenous Cu²⁺ and Zn²⁺ or exposure to non-physiological toxic metal ions.

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Abbreviations: AMFE, anomalous mole fraction effect; Asp, aspartic acid residue; CaM, calmodulin; CDI, Ca²⁺-dependent inactivation; Glu, glutamic acid residue; Gly, glycine residue; His, histidine residue; HVA, high voltage activated; IV, macroscopic steady-state current–voltage relationship; IIV, macroscopic instantaneous current–voltage relationship; IVA, intermediate voltage activated; LVA, low voltage activated; p-loop, pore loop; VDI, voltage-dependent inactivation; VGCCs, voltage-gated calcium channels.

* Corresponding authors at: University of Cologne, Institute for Neurophysiology, Robert-Koch-Str. 39, D-50931 Köln, Germany. Tel.: +49 221 4786946; fax: +49 221 4786965.

E-mail addresses: felix@neumaier-net.de (F. Neumaier), Toni.Schneider@uni-koeln.de (T. Schneider).

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1. Introduction

Voltage-gated Ca²⁺-channels (VGCCs) are unique among the superfamily of voltage-gated ion channels, as they are not only involved in electrical signalling but also provide the key link between electrical signals and non-electrical processes, such as transmitter release, muscle contraction and transcription (Table 1) (Catterall, 1998; Hofmann et al., 1999). They respond to membrane potential changes and allow selective influx of Ca²⁺, which can either serve to activate Ca²⁺-dependent intracellular processes or shape the electrical properties of

excitable cells. The diverse functional roles of VGCCs in different tissues are well established and have been reviewed in several excellent articles (Catterall, 2011; Senatore et al., 2012; Hofmann et al., 2014; Simms and Zamponi, 2014), but many fundamental questions regarding the mechanisms by which these channels achieve high rates of voltage-dependent and Ca²⁺-selective flux remain unanswered. Recent construction and crystallographic analysis of the Ca²⁺-selective bacterial model channel Ca_vAb provide a structural framework for understanding channel function, and this reveals a mechanism of selective permeation which may be shared by eukaryotic channels. It is

Table 1
Classification of native Ca²⁺ currents and cloned α₁-subunits.

Native current	Organic or polypeptide antagonist ^a	Cloned α ₁ -subunit	Proposed cellular functions
L-type	Dihydropyridines	Ca_v1.1 (α _{1S})	Excitation–contraction coupling
	Phenylalkylamines	Ca_v1.2 (α _{1C})	Excitation–contraction coupling, excitation–transcription coupling, synaptic integration, hormone release
	Benzothiazepines	Ca_v1.3 (α _{1D})	Cardiac pacemaking, synaptic regulation, excitation–transcription coupling, hormone release, hearing
	Calciseptine, FS2	Ca_v1.4 (α _{1F})	Transmitter release (photoreceptors)
P/Q-type	ω-Agatoxins IVA & B	Ca_v2.1 (α _{1A})	Transmitter release, hormone release, dendritic Ca ²⁺ -transients
	ω-Conotoxins MVIIC & D		
N-type	ω-Conotoxins CVIA & D ω-Conotoxin GVIA & MVIIA	Ca_v2.2 (α _{1B})	Transmitter release, hormone release, dendritic Ca ²⁺ -transients
R-type	SNX-482	Ca_v2.3 (α _{1E}) + Ca _v x?	Pacemaking, transmitter release, LTP, repetitive firing, Ca ²⁺ -transients
T-type	(+) -ECN (Kurt toxin)	Ca_v3.1 (α _{1G})	Pacemaking, repetitive firing
		Ca_v3.2 (α _{1H})	Pacemaking, repetitive firing
		Ca_v3.3 (α _{1I})	Pacemaking, repetitive firing

Source: McDonough (2004), Snutch et al. (2005), Striessnig and Koschak (2008), Catterall et al. (2013), Schneider et al. (2013).

^a Note that most of the listed agents are not perfectly selective and affect more than a single type of VGCC, especially at saturating concentrations.

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